Preliminary Report on the Effect of a Lower Dose of Gonadotropin-releasing Hormone Antagonist (Cetrorelix) on Ovarian Hyperstimulation in Lower-weight Asian Women

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SUMMARY

Objective: To determine the minimal effective daily dose of gonadotropin-releasing hormone (GnRH) antagonist in lower-weight Asian women undergoing controlled ovarian hyperstimulation (COH).

Materials and Methods: A prospective randomized controlled trial of GnRH antagonist was performed. A total of 58 women with body weight of 40–50 kg accepted COH and transvaginal embryo transfer. Patients were divided into two groups: Group 1 patients ($n=28$) were given a fixed cetrorelix dose of 0.2 mg/day; Group 2 patients ($n=30$) were given a fixed cetrorelix dose of 0.15 mg/day. Cetrorelix was administered from menstrual day 8 until the day of human chorionic gonadotropin (hCG) administration. Serum luteinizing hormone (LH) and estradiol (E2) concentration were measured on the day of hCG administration. Gonadotropin dosages, LH and E2 concentrations, retrieved oocyte and embryo numbers, ovarian hyperstimulation syndrome (OHSS), embryo quality, and the rates of fertilization, implantation and pregnancy in both groups were compared.

Results: The clinical pregnancy/implantation rates in Group 1 were higher than those in Group 2 (28.6%/10.4% *vs.* 20%/4.1%). The numbers of oocytes retrieved/Grade I–II embryos were higher in Group 1 than Group 2 (10.5/7.8 *vs.* 8.3/3.9). A lower percentage of LH surge and higher E2 levels on the day of hCG adminstration were observed in Group 1 compared to Group 2 (5.9%/1,610.8 pg/mL *vs.* 26.7%/1,023.6 pg/mL). There were no statistical differences between the two groups when comparing gonadotropin dosage and OHSS.

Conclusion: The lowest effective dosage of cetrorelix is 0.2 mg in COH and pituitary downregulation for lower-weight Asian women. [*Taiwanese J Obstet Gynecol* 2006;45(4):317–320]

Key Words: cetrorelix, GnRH antagonist, IVF, ovarian hyperstimulation, pituitary downregulation

Introduction

In current practice, gonadotropin-releasing hormone (GnRH) analogs are widely used to suppress endogenous gonadotropins during ovarian stimulation. The "long protocol" is generally the most effective and most popular in controlled ovarian hyperstimulation (COH). Major disadvantages of GnRH analogs are increased gonadotropin dosage after prolonged pituitary suppression and higher risk of ovarian hyperstimulation syndrome (OHSS) [1]. GnRH analogs desensitize the pituitary gonadotropin cell and reduce the number of GnRH receptors. Furthermore, GnRH analogs initially stimulate the release of gonadotropins (flare-up) and complete pituitary suppression is only achieved after 2–3 weeks pretreatment when pituitary desensitization occurs due to receptor downregulation.

Recently, GnRH antagonists have been used to prevent the onset of premature luteinizing hormone (LH)

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surges during COH. GnRH antagonists allow a short and simple treatment regimen for *in vitro* fertilization (IVF) patients. GnRH antagonists act by competing with native GnRH for GnRH receptor binding sites, resulting in rapid suppression of gonadotropins. Another advantage of GnRH antagonists is reduction of gonadotropin dosage during ovarian stimulation programs and lower risk of OHSS [2]. GnRH antagonists greatly reduce the duration of pituitary downregulation and prevent adverse events related to flare-up induced by GnRH analogs.

Development of third- and fourth-generation GnRH antagonists have obtained favorable clinical results. Cetrorelix (ASTA Medica GmbH, Frankfurt/Main, Germany) or ganirelix (Organon, Oss, The Netherlands) have been used in recent clinical studies [3,4]. Daily administration of the GnRH antagonist (the so-called multiple dose protocol) at its minimum effective dose (0.25 mg/day subcutaneously) has been proven to be safe and effective [5,6]. Clinical research on cetrorelix started off with relatively high daily doses of 3 and 1 mg [3,4], but finally, the lowest effective daily dose appeared to be 0.25 mg [6,7]. However, few studies report trials of GnRH antagonists in Asians. There is no literature dealing with GnRH antagonist doses ≤ 0.2 mg for pituitary suppression during COH.

Furthermore, results from clinical trials of the use of GnRH antagonists in Asian women are few. In general, Asian women weigh less than Caucasian women. Given racial and ethnic differences, it is logical to suspect that Asians and Caucasians require different effective GnRH antagonist doses. Therefore, we aimed to determine the minimum safe and effective dose of GnRH antagonist for pituitary suppression in lower-weight Asian women. To the best of our knowledge, this is one of the first such reports in this field.

Materials and Methods

This trial was a phase III, open-label, prospectively randomized study to assess the efficacy and safety of GnRH antagonists in women undergoing COH. A total of 58 females from infertile couples who accepted COH, IVF with intracytoplasmic sperm injection (ICSI) and transvaginal embryo transfer (TV-ET) were included. Main inclusion criteria were: age at least 18 years but not older than 39 years; body weight between 40 and 50 kg; regular menstrual period, ranging from 24 to 35 days. Approval from the institutional review board was obtained for the analysis of this series.

All patients who accepted cetrorelix (Serono, Rome, Italy) were divided randomly into two groups: Group 1 patients ($n = 28$) were given a fixed cetrorelix dose of 0.2 mg/day; Group 2 patients ($n = 30$) were given a fixed cetrorelix dose of 0.15 mg/day. Cetrorelix was administered from menstrual day 8 until the day of human chorionic gonadotropin (hCG) administration. The COH protocol performed in both groups was as previously described [8]. In brief, during menstrual days 3–7, younger patients (< 35 years old) took two ampules (150 IU) of Gonal-F (Serono) daily, and older patients (≥ 35 years old) took three ampules (225 IU) of Gonal-F daily. Ultrasound examination and measurements for serum estradiol (E2), follicle stimulating hormone (FSH) and LH levels were performed on menstrual days 3, 8, 10 and 12. If day 8 E2 was < 100 pg/mL, then the daily gonadotropins were increased to three ampules (225 IU) of Gonal-F for younger patients and four ampules (300 IU) of Gonal-F for older patients. Criteria for cancellation included lower E2 level on menstrual day 8 (< 50 pg/mL) and poor follicle growth during COH.

Gonadotropin and cetrorelix administration continued until two or more follicles measured > 18 mm; then hCG 5,000 IU (Serono) was administered. Serum LH and E2 concentrations were tested on the day of hCG administration. Oocytes were retrieved transvaginally 34–36 hours later. Oocyte culture, insemination, embryo transfer and cryopreservation were as previously described [9]. TV-ET was performed 72 hours after oocyte retrieval. A maximum of four embryos were transferred into each patient. Luteal phase was supported with hCG (2,500 IU/day) on days 1, 4 and 7 post-ET, and progesterone 400 mg (Utrogeston®) from day 1 post-ET. Clinical pregnancy was defined as elevated serum β-hCG 12 days after ET and visualization of a gestational sac by ultrasound.

Personal data (age, weight, body mass index, cause of infertility), gonadotropin dosage, and serum concentration of LH and E2 on the day of hCG administration of the two groups were compared. Retrieved oocyte and embryo numbers, development of OHSS, embryo quality, and the rates of fertilization, implantation and pregnancy in both groups were assessed and compared. SAS software (SAS Institute Inc., Cary, NC, USA) with *t* test and χ^2 test were utilized for statistical analyses. A p value < 0.05 was considered statistically significant.

Results

We observed a favorable outcome in Group 1 (0.2 mg cetrorelix). The clinical pregnancy/implantation rates in Group 1 were higher than those in Group 2 (28.6%/10.4% *vs.* 20%/4.1%; Table). Furthermore, Group 1

Table. Comparisons of gonadotropin-releasing hormone (GnRH) antagonist dosages, gonadotropin dosages, laboratory data, ovarian hyperstimulation syndrome (OHSS), and clinical results in both groups

Variable	Group 1 (Cetrorelix 0.2 mg; *n* = 28)	Group 2 (Cetrorelix 0.15 mg; *n* = 30)	*p*
Age	30.96 ± 2.92	30.07 ± 3.63	NS
BMI	19.21 ± 0.81	19.15 ± 0.84	NS
GnRH antagonist dosage	1.07 ± 0.28	0.763 ± 0.147	< 0.05*
Gonadotropin dosage	1,669.6 ± 409.3	1,856.7 ± 733.9	NS*
Oocytes retrieved, *n*	10.5 ± 5.1	8.3 ± 6.7	< 0.05*
Oocytes fertilized, *n*	9.2 ± 4.2	5.1 ± 2.4	< 0.05*
Grade I/II embryos	7.8 ± 4.8	3.9 ± 2.4	< 0.05*
E2 on hCG day (pg/mL)	1,610.8	1,023.6	< 0.05*
LH surge, *n* (%)	2 (5.9)	8 (26.7)	< 0.05*
Chemical pregnancy, *n* (%)	10 (35.7)	7 (23.3)	< 0.05*
Clinical pregnancy, *n* (%)	8 (28.6)	6 (20)	< 0.05*
Implantation rate (%)	10.4	4.1	< 0.05*
OHSS	0	0	NS†

**t test; †χ^2 test. BMI = body mass index; E2 = estradiol; hCG = human chorionic gonadotropin; LH = luteinizing hormone; NS = non-significant difference.*

patients also appeared to have better quality embryos and oocytes. The numbers of oocytes retrieved/grade I–II embryos in Group 1 were higher than those in Group 2 (10.5/7.8 *vs.* 8.3/3.9). A lower percentage of LH surge and higher E2 levels on the day of hCG adminstration were observed in Group 1 compared to Group 2 (5.9%/1,610.8 pg/mL *vs.* 26.7%/1,023.6 pg/mL; Table). There were no statistical differences between the two groups in mean age, causes and duration of infertility, baseline FSH concentration, cancellation rate, gonadotropin dosage and OHSS.

Discussion

GnRH antagonists have been developed in parallel with GnRH analogs, but their development history has been plagued by high incidences of histamine release following injection. Over the past few years, prevention of histamine-releasing activity has been achieved. Third-generation GnRH antagonists (cetrorelix and ganirelix) have been used in multiple-dose regimens in women undergoing COH. Since antagonists immediately suppress gonadotropins by blocking GnRH receptors, treatment may be restricted to those days when premature LH surge is likely to occur. Investigators have demonstrated that serum GnRH antagonist concentrations increase in a linear dose-proportional manner and serum LH decreases in a dose-proportional manner [10,11].

Recent studies revealed that maximal endogenous LH suppression occurs about 4 hours after GnRH antagonist administation [11]. Moreover, rapid recovery of pituitary function was observed after discontinuation of the GnRH antagonist [12]. This is due to the relatively short elimination half-life (about 13 hours) of GnRH antagonists [5]. These results suggest that the degree of pituitary suppression can be adjusted by changing the GnRH antagonist dose. However, controversy remains about the real efficacy of GnRH antagonist application. Some investigators demonstrated decreased pregnancy rates in GnRH antagonist cycles [13,14].

The advantages of GnRH antagonist treatment in ovarian stimulation programs are reduced dosage of gonadotropins and lower risk of OHSS. The minimum dose necessary to suppress LH release without impairing embryo development and implantation may be determined. To select the minimum effective daily dose of a GnRH antagonist, a multicenter, double-blind, randomized, dose-finding study was performed on 333 women and included six different dosages ranging from 0.0625 to 2 mg [13,15]. This study showed that a daily dose of 0.25 mg GnRH antagonist was a safe, short and convenient treatment regimen for women undergoing COH, and resulted in good clinical outcome [13]. Borm and Mannaerts demonstrated that a daily dose of 0.25 mg GnRH antagonist prevented LH surge and led to a favorable outcome (37% ongoing pregnancy rate) [5]. Few authors have reported a dosage of GnRH antagonist ≤ 0.2 mg in pituitary suppression.

Regarding racial differences, most Asian women appear to weigh less than Caucasian women. Therefore, the GnRH antagonist dosage should be adjusted. In this series, we first tried a lower dose for Asians with a lower body weight. We observed that individuals with

a lower body weight (< 50 kg) should be considered for a 0.2 mg daily dosage of cetrorelix. We also noted that cetrorelix 0.15 mg daily is not suitable for LH suppression. In this study, we noted that clinical pregnancy/implantation rates in the 0.2 mg group were higher than those in the 0.15 mg group. We also noted that 0.2 mg cetrorelix appeared to have a comparable pregnancy rate (around 30%) to that of 0.25 mg cetrorelix found in previous studies [5,16]. The LH surge risk for the 0.2 mg daily dose was as low as that of the 0.25 mg trials.

In conclusion, 0.2 mg cetrorelix might be the lowest effective dose in COH and pituitary downregulation for lower-weight Asian women. A lower dosage of cetrorelix might be unsuitable for pituitary suppression. A dosage of 0.2 mg cetrorelix should be considered for individuals with a lower body weight. Regarding case number limitation, a larger series might be necessary to clarify related issues. Furthermore, the influence of GnRH antagonists on pregnancy rate, synchronization of follicles, and oocyte and embryo quality merits further surveys. However, a bright future for the application of GnRH antagonists is expected. Further application of GnRH antagonists will allow a short and simple treatment regimen for IVF patients undergoing COH.

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